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THE NONINVASIVE CARBON DIOXIDE GRADIENT ($NICO_2G$) DURING HEMORRHAGIC SHOCK

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ABSTRACT—Hemorrhagic shock (HS) is a setting in which both pulmonary and cutaneous perfusion may be impaired. The goals of this study were to evaluate the relationship between end-tidal ($etCO_2$), transcutaneous ($tPCO_2$), arterial carbon dioxide ($PaCO_2$) and lactate during lethal HS and to assess the effect of progressive HS on those variables and on a new variable, the noninvasive CO_2 gradient ([$NICO_2G$] or the difference between $tPCO_2$ and $etCO_2$). Ten consciously sedated swine were hemorrhaged, by means of a computerized exponential protocol, of up to 80% estimated blood volume for 20 min. End-tidal carbon dioxide, $tPCO_2$, $PaCO_2$, and lactate measurements were taken at baseline and every 5 min thereafter, that is, after 25%, 44%, and 62% total blood volume hemorrhage (TBVH) and at cardiac arrest. Cardiac arrest occurred on average at 67% TBVH. Data were analyzed by linear regression and one-way repeated-measures analysis of variance and are presented as means ± SD. Forty-nine paired measurements were made. There was no overall relationship between $NICO_2$ variables and $PaCO_2$: $PaCO_2$ vs. $tPCO_2$ ($r^2 = 0.002$, $P = 0.78$); $PaCO_2$ vs. $etCO_2$ ($r^2 = 0.0002$, $P = 0.93$). Rather, $NICO_2G$ increased at each level of blood loss: 4.0 ± 24.9 at baseline, 6.3 ± 35.7 at 25% TBVH, 25.0 ± 37.6 at 44% TBVH, 55.0 ± 33.9 at 62% TBVH, and 70.0 ± 33.2 at cardiac arrest ($P < 0.05$). Similarly, $tPCO_2$ increased and $etCO_2$ decreased at each level. Linear regression of $NICO_2G$ and lactate showed a better correlation than was observed for the other two variables: $NICO_2G$, $r^2 = 0.58$; $tPCO_2$, $r^2 = 0.46$; $etCO_2$, $r^2 = 0.26$. During HS, $NICO_2$ monitors lose accuracy for approximating the $PaCO_2$ but gain usefulness as hemodynamic monitors. Also, by combining data from two different organ systems, $NICO_2G$ demonstrated improved correlation with lactate than did either $etCO_2$ or $tPCO_2$ alone.

KEYWORDS—Transcutaneous carbon dioxide, end-tidal carbon dioxide, noninvasive carbon dioxide gradient, blood gas analysis, hemorrhage, swine

INTRODUCTION

Current recommendations for the management of trauma and post–cardiac arrest (CA) patients place significant emphasis on the maintenance of adequate ventilation and on the avoidance of hypocapnia or hypercapnia (1–3). To facilitate this, when arterial blood gas measurements are not readily available, two main types of noninvasive CO_2 ($NICO_2$) technologies have been developed: end-tidal ($etCO_2$) and transcutaneous CO_2 ($tPCO_2$) monitors.

End-tidal CO_2 monitoring has been encouraged in patients with traumatic brain injuries, targeting the range of 25 to 35 mmHg (3–5). However, $etCO_2$ does not always correlate linearly with $PaCO_2$ because a rise in physiologic dead space or a decrease in pulmonary perfusion results in an increase in the $PaCO_2$-$etCO_2$ gradient (6). Several recent studies conducted in emergency departments revealed a poor correlation between $etCO_2$ and $PaCO_2$ in severely injured patients (7) as well as in nontrauma patients (8, 9).

An alternative $NICO_2$ monitoring technique uses transcutaneous measurements of the partial pressure of CO_2 ($tPCO_2$). Several studies reported a good correlation between $tPCO_2$ and $PaCO_2$ in adults under general anesthesia (10, 11). Similar results were described in critically ill patients (12–14). In addition, $tPCO_2$ appears to be a more accurate noninvasive substitute for $PaCO_2$ than $etCO_2$ in critically ill patients during interhospital transfer (15). However, decreased skin perfusion, for example, during hypovolemic shock, alters $tPCO_2$ relationship with $PaCO_2$.

Increasingly, both techniques are recognized not only as noninvasive correlates of $PaCO_2$ but also as indicators of the adequacy of pulmonary ($etCO_2$) and cutaneous ($tPCO_2$) perfusion. Several guidelines recommend using end-tidal capnometry for assessment of the adequacy of cardiopulmonary resuscitation and of the return of spontaneous circulation (1). It has been reported that during emergency trauma surgery, $etCO_2$ more than 27 mmHg and $PaCO_2$-$etCO_2$ gap less than 9 mmHg predicted survival (16). Alternatively, high $tPCO_2$ levels (>60 mmHg) were associated with 90% mortality in severely injured patients (17). In addition, an elevated $tPCO_2$-$etCO_2$ gap more than 26 mmHg as well as a $tPCO_2$-$PaCO_2$ gap more than 16 mmHg were reported to be associated with poor outcomes in patients with septic shock (18).

Previously, our group performed a series of animal experiments to better understand the utility of these $NICO_2$ monitoring techniques. Swine models were chosen because their physiology

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14. ABSTRACT

Purpose: Hemorrhagic shock (HS) is a setting in which both pulmonary and cutaneous perfusion may be impaired. The goals of this study were (1) to evaluate the relationship between end-tidal (etCO2), transcutaneous (tPCO2), arterial carbon dioxide (PaCO2), and lactate during lethal HS; and (2) to assess the effect of progressive HS on those variables and on a new variable, the "non-invasive CO2 gradient" (NICO2G, or difference between tPCO2 and etCO2). Materials and Methods: Ten consciously sedated swine were hemorrhaged, by means of an computerized exponential protocol, of up to 80% estimated blood volume (EBV) over 20 min. EtCO2, tPCO2, PaCO2, and lactate measurements were taken at baseline and every 5 min thereafter, i.e., after 25%, 44%, and 62% total blood volume hemorrhage (TBVH), and at cardiac arrest (CA). CA occurred on average at 67% TBVH. Data were analyzed by linear regression and one-way repeated measures analysis of variance (ANOVA) and are presented as means +/- SD. Results: 49 paired measurements were made. There was no overall relationship between non-invasive CO2 variables and PaCO2: PaCO2 vs. tPCO2 ($r^2 = 0.002$; $p = 0.78$); PaCO2 vs. etCO2 ($r^2 = 0.0002$; $p = 0.93$). Rather, NICO2G increased at each level of blood loss: 4.0+/-24.9 at baseline, 6.3+/-35.7 at 25% TBVH, 25.0+/-37.6 at 44% TBVH, 55.0+/-33.9 at 62% TBVH, and 70.0+/-33.2 at CA ($p < 0.05$). Similarly, tPCO2 increased and etCO2 decreased at each level. Linear regression of NICO2G and lactate showed a better correlation than was observed for the other 2 variables: NICO2G $r^2 = 0.58$; tPCO2 $r^2 = 0.46$; etCO2 $r^2 = 0.26$. Conclusions: During HS, non-invasive CO2 monitors lose accuracy for approximating the PaCO2, but gain usefulness as hemodynamic monitors. Also, by combining data from 2 different organ systems, NICO2G demonstrated improved correlation with lactate than did either etCO2 or tPCO2 alone. (C) 2014 by the Shock Society.

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closely resembles that of humans. First, we explored the relationship between $etCO_2$ and $PaCO_2$ over a wide range of ventilator settings in a swine model of pulmonary contusion and hemorrhage. Before injury and, later, after resuscitation, there was an excellent correlation. During the immediate period after injury and during hemorrhage, this relationship broke down (19). Second, we evaluated both $etCO_2$ and $tPCO_2$ in a swine model of acute lung injury secondary to smoke inhalation injury and burns. We demonstrated that $tPCO_2$ monitoring was an acceptable surrogate for $PaCO_2$ under hemodynamically stable conditions but not during periods of hemodynamic instability. We also found that the relationship between $etCO_2$ and $PaCO_2$ was less linear early after lung injury and during rapid changes in lung function (20).

Based on these findings, we decided to further explore the effect of shock on $etCO_2$ and $tPCO_2$. The present study extends our previous work by collecting data at several steps during a hemorrhage process that is, ultimately, lethal. In addition, we described the $NICO_2$ gradient ($NICO_2G$), which we define as the difference between $etCO_2$ and $tPCO_2$. It takes advantage of the dual observations that $etCO_2$ decreases (16) and $tPCO_2$ increases (17) during hypovolemic shock, reminiscent of the work of Vallee and colleagues (18). We had two questions: 1) Can $etCO_2$ and/or $tPCO_2$ serve as surrogates for $PaCO_2$ in an exsanguinating subject? 2) Does $etCO_2$, $tPCO_2$, or $NICO_2G$ correlate with the severity of hemorrhage-induced metabolic debt, as indicated by elevated arterial lactate? By addressing these questions, we aimed to better understand the utility and limitations of $NICO_2$ monitoring under conditions of life-threatening hemorrhagic shock (HS). Also, arterial lactate more than 4 mmol/L has been associated with hypoperfusion and with increased mortality (21); lactate has been used as a resuscitation index (22). Thus, in the present study, we also sought to understand the relationship between $NICO_2$ variables and lactate.

MATERIALS AND METHODS

This study was approved by the US Army Institute of Surgical Research Animal Care and Use Committee. It was conducted in compliance with the Animal Welfare Act and the implementing Animal Welfare Regulations and in accordance with the principles of the *Guide for the Care and Use of Laboratory Animals*.

Animal preparation

For this study, we used a convenience sample collected prospectively from the first 10 consecutive animals used in the larger study of exsanguination and CA caused by lethal hemorrhage. All 19 animals from the parent protocol were female nonpregnant Yorkshire pigs, purchased from Midwest Research Swine (Gibbon, Minn), *Sus scrofa* species, and bred for research. The parent protocol consisted of a single group of animals instrumented and treated identically. Animals were fasted overnight with water *ad libitum*. At the beginning of the experiment, animals were anesthetized with Telazol (tiletamine/zolazepam 4 – 6 mg/kg) by i.m. injection. Analgesia was provided using buprenorphine hydrochloride i.m. (0.25 mg/kg). Venous access was established with an 18- to 22-gauge catheter placed in a peripheral ear vein. Subsequently, animals were endotracheally intubated, and anesthesia was maintained during the surgical procedure using isoflurane (2% – 4%) in 100% oxygen. The animals were placed supine on the operating table for surgical instrumentation. Surgery included tracheostomy and placement of catheters in an external jugular vein, carotid artery, femoral artery, and femoral vein. In addition, surgical steel wires were placed subcutaneously for electrocardiography in a lead II configuration. Before placement, the tissues around the catheter and steel wire sites were infiltrated with 2% bupivacaine for local anesthesia. To assess the level of sedation, bispectral index (BIS) electrodes (Aspect Medical Systems, Newton, Mass) were placed on the forehead.

After completion of the surgical procedure, isoflurane was discontinued and continuous i.v. infusion of midazolam (0.6 – 2.5 mg/kg per h) was initiated to maintain conscious sedation titrated to a BIS level of 70 to 80. Postprocedurally, analgesia coverage was provided by the buprenorphine hydrochloride i.m. and 2% bupivacaine local injections administered earlier. In all 10 animals enrolled in this study, the SenTec digital monitor with V-sign sensor (SenTec Ag, Therwil, Switzerland) were used for $tPCO_2$ monitoring. The V-sign sensor was attached to the right auricle using a single-use attachment ring. Before the sensor placement, the area was cleansed with isopropyl alcohol. One drop of SenTec contact gel was applied to the center of the membrane. The V-sign sensor was heated to 43.5°C during use. A Capnostream 20 device with a FilterLine H Set CO_2 sidestream sampling line and an airway adapter (Oridion Medical, Jerusalem, Israel) were used for $etCO_2$ monitoring. Arterial blood gas analysis was performed with i-STAT system (Abbot Point of Care, Princeton, NJ). CG4 cartridges were used to measure pH, $PaCO_2$, and lactate values.

After surgery, animals were recovered for approximately 30 min. A set of baseline measurements was taken. Animals were then bled up to 80% of the estimated blood volume for 20 min using the computerized exponential protocol previously described by Burns et al. (23) (Fig. 1). A computer-controlled withdrawal system, based on a Masterflex peristaltic pump (Thermo Fisher Scientific, Waltham, Mass), was used for the hemorrhage. Throughout the experiment, animals were allowed to breathe spontaneously on continuous positive airway pressure at 5 cm H_2O. Once an animal developed respiratory arrest, defined as a respiratory rate less than 6 breaths per minute or a minute ventilation less than 25% of the baseline for more than 30 s, controlled mechanical ventilation was initiated with a tidal volume of 10 mL/kg, a fraction of inspired oxygen (FiO_2) of 100%, and a respiratory rate adjusted between 12 and 20 breaths per min to maintain $PaCO_2$ between 35 and 45 mmHg. Arterial blood gas samples and corresponding $tPCO_2$ and $etCO_2$ values were recorded at baseline, at 5 min (~25% total blood volume hemorrhage [TBVH]), at 10 min (~44% TBVH), at 15 min (~62% TBVH), and at CA (~67% TBVH). Cardiac arrest was defined as a sustained aortic diastolic pressure of 20 mmHg or less, as measured by the Millar transducer. The study was terminated at death, which was defined as a mean arterial pressure of 0 mmHg and an $etCO_2$ less than 8 mmHg.

Statistical analysis

Analyses were performed using SigmaPlot Version 12.0 for Windows (Systat Software, San Jose, Calif) and SAS version 9.2 (SAS Institute Inc., Cary, NC). Linear regression and Bland-Altman analysis were used to determine the correlation between $PaCO_2$ and several continuous variables, to include $tPCO_2$ and $etCO_2$. Variables were tested for normality using the Shapiro-Wilk test. One-way repeated-measures analysis of variance (ANOVA) with *post hoc* Dunnett tests were used to analyze changes over time for normally distributed data. Those that did not meet the criteria for normality were analyzed using Friedman nonparametric test for repeated measures. Fisher exact test was used to

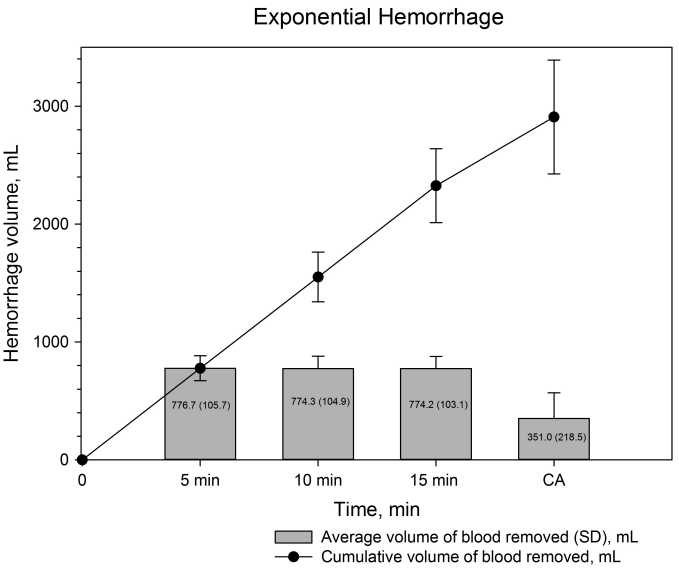

FIG. 1. **Exponential hemorrhage volume in milliliters recorded after 25%, 44%, and 62% TBVH and at CA.**

TABLE 1. **Vital sign and blood gas changes during hemorrhage**

	Baseline	25% TBVH	44% TBVH	62% TBVH	CA
Temp	38.5 ± 0.5	38.6 ± 0.7	38.7 ± 0.7	38.8 ± 0.7	38.6 ± 0.8
HR	104.2 ± 25.2	116.1 ± 32.3‖	128.3 ± 34.0‖	160.9 ± 56.1	116.2 ± 79.0
MAP	102.3 ± 16.0	67.1 ± 15.4‡	43.5 ± 20.3‡	26.7 ± 13.7‡	10.5 ± 13.6‡
CVP	5.3 ± 5.2	1.0 ± 3.6§	0.9 ± 4.7§	2.1 ± 5.9‖	1.2 ± 3.0
PAP	19.8 ± 5.3	11.5 ± 8.1§	15.1 ± 17.3§	11.6 ± 5.9§	7.3 ± 5.1‖
Arterial pH	7.32 ± 0.07	6.88 ± 1.0	7.24 ± 0.27	7.33 ± 0.11	7.19 ± 0.36
Lactate	4.0 ± 2.8	4.3 ± 3.2	5.5 ± 3.1	7.7 ± 2.9§	7.8 ± 2.4§
$PaCO_2$	51.8 ± 3.7	60.5 ± 23.2	51.3 ± 25.8	38.9 ± 15.7	54.7 ± 38.6
$PmvCO_2$	59.0 ± 5.2	54.5 ± 13.1	61.9 ± 14.2	66.7 ± 22.0	75.9 ± 20.4‖
$tPCO_2$	56.2 ± 23.1	54.9 ± 33.7	61.9 ± 35.0	75.7 ± 35.2†	78.3 ± 35.5‡
$etCO_2$	52.2 ± 5.2	48.6 ± 5.4	36.9 ± 7.2‡	20.8 ± 12.0‡	8.3 ± 7.2‡

TBVH indicates total blood volume hemorrhage; CA, cardiac arrest; Temp, core body temperature (in degrees Celsius); HR, heart rate; MAP, mean arterial pressure (in millimeters mercury); CVP, central venous pressure (in millimeters mercury); PAP, mean pulmonary artery pressure (in millimeters mercury); BE, arterial base excess (in millimolar); Lactate, arterial lactate level (in millimolar); $PaCO_2$, arterial pressure of carbon dioxide (in millimeters mercury); $PmvCO_2$, partial pressure of carbon dioxide in mixed venous blood (in millimeters mercury); $tPCO_2$, transcutaneous carbon dioxide (in millimeters mercury); $etCO_2$, end-tidal carbon dioxide (in millimeters mercury).
*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ by ANOVA with *post hoc* Dunnett tests compared with baseline.
§$P < 0.05$; ‖$P < 0.01$ by Friedman test compared with baseline.

compare categorical variables. All results are expressed as means ± SD. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Data were recorded from 10 animals with an average weight of 61.9 ± 10.3 kg. Average time to CA was 22 min 19 sec ± 4 min 2 sec. Average blood loss at CA was 67% ± 9% of the estimated TBV. Measurements (n = 49) of $PaCO_2$, $tPCO_2$, and $etCO_2$ were recorded. Figure 1 demonstrates cumulative hemorrhage volumes during the experiment. Table 1 presents vital signs and laboratory values with data grouped and evaluated based on the percentage of TBVH.

Linear regressions of $tPCO_2$ or $etCO_2$ with $PaCO_2$ are presented in Figure 2A. There was no relationship between $PaCO_2$ and $tPCO_2$ ($r^2 = 0.002$, $P = 0.78$). Similarly, there was no relationship between $PaCO_2$ and $etCO_2$ ($r^2 = 0.0002$, $P = 0.93$). In addition, a Bland-Altman analysis was performed. For $tPCO_2$, bias was −13.5 ± 41.8 mmHg (Fig. 2B). For $etCO_2$, bias was 18.1 ± 30.4 mmHg (Fig. 2C).

Changes over time in various gradients, to include the $NICO_2G$, are presented in Table 2. Figure 3 illustrates the observed divergence between $tPCO_2$, $etCO_2$, and $NICO_2G$ values with each hemorrhage step.

Linear regression of $etCO_2$, $tPCO_2$, and $NICO_2G$ with lactate was also performed. These data are presented in Figure 4, A to C. Here, note that the correlation for $etCO_2$ was quite low, $r^2 = 0.26$ ($P < 0.001$); for $tPCO_2$, it was better, $r^2 = 0.46$ ($P < 0.001$); and for $NICO_2G$, it was best, $r^2 = 0.58$ ($P < 0.0001$).

In view of the observed relationship between $NICO_2G$ and lactate, the variables were categorized into dichotomies, as follows: lactate greater than or less than 4 mmol/L; $NICO_2G$ greater than or less than 0; $tPCO_2$ greater than or less than 50 mmHg; and $etCO_2$ greater than or less than 20 mmHg. A Fisher exact test was performed, which disclosed that the relationships between lactate and the other categorical variables were highly significant ($P < 0.001$). Noninvasive CO_2G greater than 0 had a sensitivity of 88%, a specificity of 73%, and an accuracy of 85% for detecting lactate greater than 4 mmol/L. In

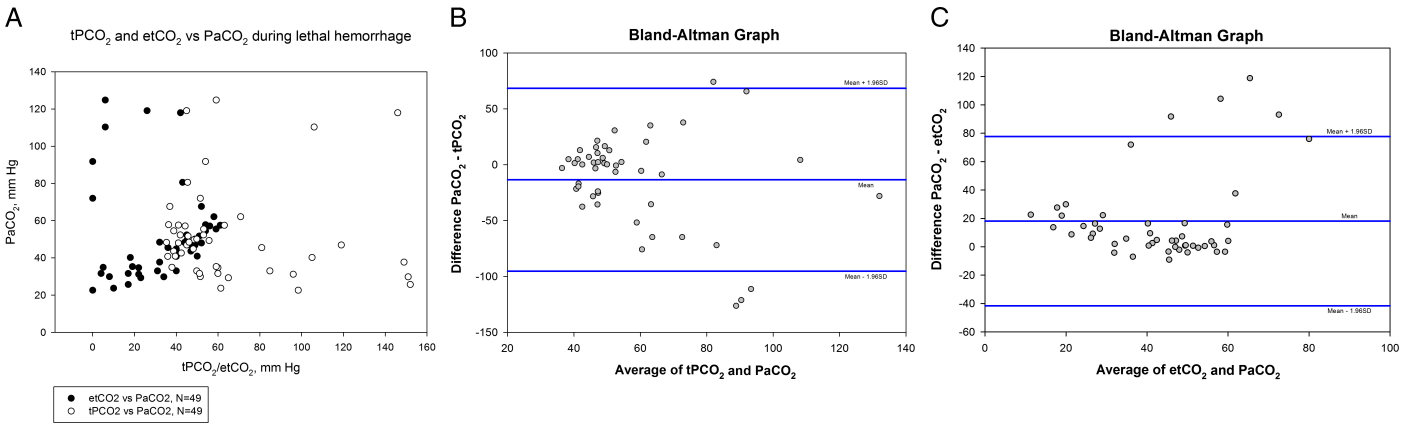

FIG. 2. **A, Linear regression of $PaCO_2$ and $tPCO_2$ or $etCO_2$ (n = 49)**. Neither $tPCO_2$ ($r^2 = 0.002$, $P = 0.78$) nor $etCO_2$ ($r^2 = 0.0002$, $P = 0.93$) correlated with $PaCO_2$. B and C, Bland-Altman analysis of $PaCO_2$ and $tPCO_2$ or $etCO_2$. The middle solid line represents the mean difference (bias), and the outer solid lines represent limits of agreement (mean ± 1.96 SD) between the two methods. For $tPCO_2$, bias was -13.5 ± 41.8 mmHg; for $etCO_2$, it was 18.1 ± 30.4 mmHg (n = 49).

TABLE 2. **CO_2 gradients during hemorrhage**

	Baseline	25% TBVH	44% TBVH	62% TBVH	CA
$NICO_2G$	4.0 ± 24.9	6.3 ± 35.7	25.0 ± 37.6*	55.0 ± 33.9‡	70.0 ± 33.2‡
$PaCO_2$-$tPCO_2$	−4.4 ± 24.6	1.6 ± 18.0	−14.2 ± 48.8	−34.9 ± 45.5	−27.3 ± 53.8
$PaCO_2$-$etCO_2$	−0.4 ± 2.6	7.9 ± 24.6	10.8 ± 28.0	20.1 ± 24.8§	42.7 ± 38.9‖
$PaCO_2$-$PmvCO_2$	−7.2 ± 2.2	7.5 ± 27.1	−8.6 ± 31.2	−24.5 ± 18.7	−34.6 ± 14.9¶

TBVH indicates total blood volume hemorrhage; CA, cardiac arrest; $NICO_2G$, noninvasive carbon dioxide gradient, that is, $tPCO_2$-$etCO_2$ (in millimeters mercury); $PaCO_2$, partial pressure of carbon dioxide in arterial blood (in millimeters mercury); $tPCO_2$, transcutaneous carbon dioxide (in millimeters mercury); $etCO_2$, end-tidal carbon dioxide (in millimeters mercury); $PmvCO_2$, partial pressure of carbon dioxide in mixed venous blood (in millimeters mercury).
*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ by ANOVA with *post hoc* Dunnett tests compared with baseline.
§$P < 0.05$; ‖$P < 0.01$; ¶$P < 0.001$ by Friedman test compared with baseline.

addition, $tPCO_2$ greater than 50 mmHg had a sensitivity of 89%, a specificity of 57%, and an accuracy of 75% for detecting lactate greater than 4 mmol/L. Finally, $etCO_2$ less than 20 mmHg had a sensitivity of 100%, a specificity of 56%, and an accuracy of 60% for detecting lactate greater than 4 mmol/L.

DISCUSSION

We evaluated the utility of $NICO_2$ monitoring in an animal model of lethal hemorrhage. We found that neither $tPCO_2$ nor $etCO_2$ correlated with $PaCO_2$ in this setting. These results indicate that $NICO_2$ monitoring methods alone are not reliable for guiding ventilation management in patients who are actively exsanguinating. Rather, these sensors performed better as indicators of shock state. The $tPCO_2$ increased and the $etCO_2$ decreased with progressive blood loss. Furthermore, the $NICO_2G$, defined as the difference between $tPCO_2$ and $etCO_2$ measurements, increased with progressive hemorrhage and correlated better with arterial lactate levels than either $tPCO_2$ or $etCO_2$ alone. The sensitivity of a positive $NICO_2G$ for detecting arterial lactate level greater than 4 was 88%, and the specificity was 73%. This gradient was more accurate and specific for detecting elevated lactate (>4 mmol/L) than its individual components $tpCO_2$ and $etCO_2$.

Previous reports on the relationship between $NICO_2$ surrogates and $PaCO_2$ in critically ill patients were mixed. For example, poor $etCO_2$ correlation with $PaCO_2$ was demonstrated in severely injured intubated patients (7). On the other hand, several reports (12, 13) indicated an acceptable correlation between $tPCO_2$ and $PaCO_2$ in critically ill adults. Our own previous work in swine models indicates the utility of $etCO_2$ monitoring in patients who are stable from a hemodynamic and pulmonary standpoint. Caution should be exercised when a patient is rapidly deteriorating from either standpoint (19, 20). The present study confirms those findings in an animal model of lethal hemorrhage, that is, with hemodynamic instability taken to an extreme.

Despite encouraging results, the current generation of $tPCO_2$ monitors demonstrates some shortcomings, which include the need for frequent calibration with a tank of standardized calibration gas (24), relative bulk, need for a heated sensor, and more gradual onset of changes (compared with $etCO_2$) in response to a change in $PaCO_2$ (20). Hopefully, the next generation of $tPCO_2$ sensors, currently under development, will address several of these problems. However, like $etCO_2$, we would not expect $tPCO_2$ to serve as an effective substitute for $PaCO_2$ under conditions of severe hypovolemic shock as in the present study.

Rather, we find $etCO_2$ and $tPCO_2$ to show promise as noninvasive shock monitors. Weil and colleagues (25) were pioneers in the application of CO_2 monitoring to resuscitation. In the 1980s, they reported that the mixed-venous partial pressure of CO_2 ($PmvCO_2$) was increased and the $etCO_2$ was decreased in a porcine model of CA. They also found that cardiac output was linearly related to $etCO_2$. Thus, the difference between mixed venous and $etCO_2$ could be explained by a decreased cardiac output (decreased pulmonary blood flow) (25). Another consequence of low cardiac output is a high gradient between mixed-venous PCO_2 and arterial PCO_2 during cardiopulmonary resuscitation (26).

The CA studies led to other shock studies. Weil's group corroborated the relationship between $etCO_2$ and cardiac output in pigs with hemorrhagic, septic, and cardiogenic shock (27). Van der Linden et al. (28) demonstrated a venous-arterial gradient for PCO_2 in hemorrhaged dogs. There was an abrupt widening of this gradient when VO_2 became supply dependent, along with an increase in lactate and a decrease in $etCO_2$ (28). Dubin et al. (29) performed studies in dogs with stepwise hemorrhage. The $etCO_2$ was logarithmically related to cardiac output and linearly to CO_2 production. In other words, the greatest decrease in $etCO_2$ was seen at the lowest levels of cardiac output. This implied that, at low cardiac output, decreased $etCO_2$ may reflect

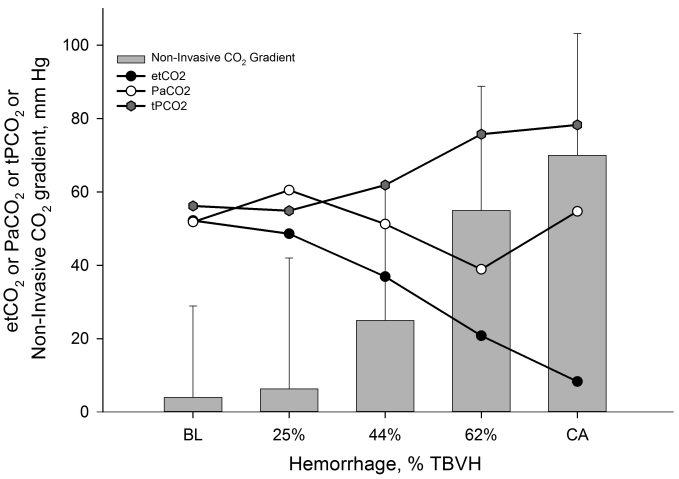

FIG. 3. **The $tPCO_2$, $etCO_2$, $PaCO_2$, and $NICO_2G$ as functions of time during hemorrhage**. For $tPCO_2$, $etCO_2$, and $PaCO_2$, means during each hemorrhage step are depicted. For $NICO_2G$, vertical bars represent means during each hemorrhage step and error bars are ±SD (n = 49).

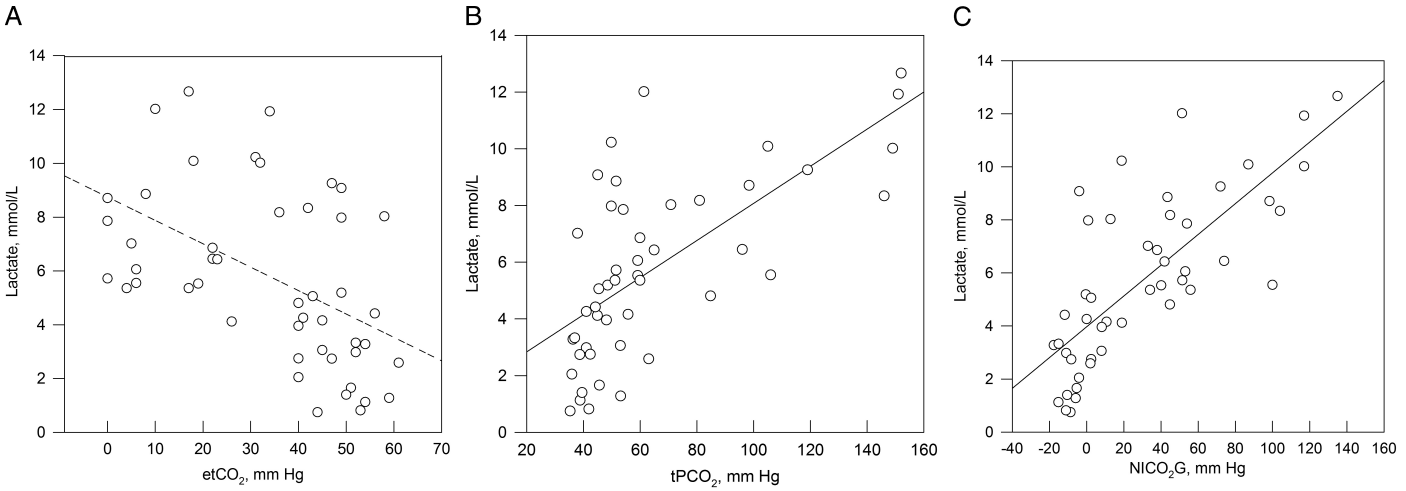

FIG. 4. **Linear regression analysis**. A, $etCO_2$ and lactate ($r^2 = 0.26$, $P < 0.001$, n = 48). B, tPCO2 and lactate ($r^2 = 0.46$, $P < 0.001$, n = 48). C, $NICO_2G$ and lactate ($r^2 = 0.58$, $P < 0.0001$, n = 48).

not only decreased pulmonary blood flow but also decreased CO_2 production (29).

In the present study, we found, like Weil and Van der Linden did, that decreases in $etCO_2$ occurred stepwise with progressive hemorrhage. We also found a widened $PaCO_2$-$PmvCO_2$ gradient, which became statistically significant at CA (Table 2). These two findings, taken together, support the concept that, in profound HS or CA, pulmonary blood flow is insufficient to maintain adequate expiration of CO_2. Clinically, this means that a falling $etCO_2$ (in a patient with a patent airway and constant ventilation) may indicate HS (or another cause of decreased pulmonary blood flow, such as a pulmonary embolism) (30, 31). Compared with other monitors, $etCO_2$ has the advantage of being continuous, referable to the central circulation, and noninvasive (32).

Recently, a prospective study of $etCO_2$ monitoring in acutely injured patients with penetrating trauma was reported, which suggests that $etCO_2$ is useful before near-arrest conditions are reached. There was a linear relationship between $etCO_2$ and lactate ($r^2 = 0.74$). The odds of operative intervention were higher in patients with a low $etCO_2$ (odds ratio, 20) than they were in patients with a high lactate (odds ratio, 4). Systolic blood pressure was related neither to the lactate level nor to the odds of operation (33). Similarly, in the present study, $etCO_2$ correlated with lactate (discussed further below).

Insofar as the skin is particularly susceptible to decreased perfusion during hypovolemic shock, $tPCO_2$ may have value as a shock monitor. Previous work by Cancio et al. (34) demonstrated decreased skin oxygenation (by hyperspectral imaging) and decreased skin blood flow (by laser Doppler imaging) during HS in pigs. The observation that $tPCO_2$ changes with HS is reminiscent of the large body of work that demonstrates the value of gastrointestinal, esophageal, and sublingual/buccal capnometry during shock and resuscitation. Transcutaneous PCO_2 monitoring would have the advantage of being entirely noninvasive and immediately accessible.

We observed that, after 25% TBVH, $tPCO_2$ measurements rose whereas $etCO_2$ values decreased. This prompted us to explore changes in the difference between the $tPCO_2$ and the $etCO_2$, or $NICO_2G$. There was a statistically significant increase in $NICO_2G$ with each subsequent hemorrhage step above 25% TBVH. Furthermore, $NICO_2G$ outperformed $etCO_2$ or $tPCO_2$ in linear regression versus lactate. As a diagnostic test for an elevated lactate (>4 mmol/L), $NICO_2G$ had an accuracy of 85%, which was higher than its individual components. We think that $NICO_2G$ performed better because it combines the features of both component variables into one. Those features are, physiologically, a decrease in pulmonary perfusion causing a decrease in the $etCO_2$ and a decrease in cutaneous perfusion causing an increase in the $tPCO_2$. Additional work is planned to evaluate the response of $NICO_2G$ to fluid resuscitation and transfusion in this hemorrhage model.

Our study had the following limitations. Animals were hypercapnic and hyperlactatemic at baseline. Most likely, these findings were caused by global hypoperfusion secondary to animals being placed and remaining in the supine position during the study. Furthermore, these animals breathed spontaneously at baseline and were placed on mechanical ventilation only after the onset of hypoventilation. The rational for avoiding mechanical ventilation at baseline was to eliminate the effect of this intervention on hemodynamics during early hemorrhage. The trade-off was that this introduced variability into animal management during the course of the experiment. On the other hand, prehospital and emergency department management of severely injured patients often does involve changes in ventilation mode, which complicate data analysis. This makes our study design more relevant to actual early trauma care.

CONCLUSIONS

This and other studies indicate that $NICO_2$ monitors provide critical information that must, however, be interpreted contextually. In this study, we demonstrated that neither transcutaneous nor end-tidal capnometry served as an accurate noninvasive $PaCO_2$ surrogate in animals sustaining rapid exsanguinating hemorrhage. Instead, a rapid drop in $etCO_2$ and/or a rise in $tPCO_2$ in a bleeding patient, whose ventilation is controlled, may indicate a critical decrease in volume status rather than a change in the $PaCO_2$ (31, 32). This concept was demonstrated in the present study by the $NICO_2G$, defined as the difference

between the $etCO_2$ and the $tPCO_2$. This gradient increased with hemorrhage and correlated well with arterial lactate levels, even as $PaCO_2$ remained constant. The $NICO_2G$ may be useful in monitoring the severity of HS.

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